

## Decolonization of intestinal carriage of extended-spectrum $\beta$ -lactamase-producing Enterobacteriaceae with oral colistin and neomycin: a randomized, double-blind, placebo-controlled trial

Benedikt Huttner<sup>1\*</sup>, Thomas Haustein<sup>1</sup>, Ilker Uçkay<sup>1</sup>, Gesuele Renzi<sup>2</sup>, Andrew Stewardson<sup>1</sup>, Danièle Schaerrer<sup>3</sup>, Americo Agostinho<sup>1</sup>, Antoine Andreumont<sup>4</sup>, Jacques Schrenzel<sup>2</sup>, Didier Pittet<sup>1</sup> and Stephan Harbarth<sup>1</sup>

<sup>1</sup>Infection Control Program, Geneva University Hospital and Faculty of Medicine, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 4, Switzerland;

<sup>2</sup>Clinical Microbiology Laboratory, Service of Infectious Diseases, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 4, Switzerland; <sup>3</sup>Pharmacy, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 4, Switzerland; <sup>4</sup>Assistance publique—Hôpitaux de Paris (AP-HP) and University Paris-Diderot Medical School, Paris, France

\*Corresponding author. Tel: +41-79-553-33-99; Fax: +41-22-372-39-87; E-mail: benedikt.huttner@hcuge.ch

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**Objectives:** Extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (ESBL-E) are an increasingly frequent cause of infections in the community and the healthcare setting. In this study, we aimed to investigate whether intestinal carriage of ESBL-E can be eradicated.

**Methods:** We conducted a double-blind, randomized, placebo-controlled, single-centre trial to assess the efficacy of an oral decolonization regimen on intestinal ESBL-E carriage in adult patients with an ESBL-E-positive rectal swab. Fifty-eight patients were allocated 1:1 to either placebo or colistin sulphate (50 mg 4×/day) and neomycin sulphate (250 mg 4×/day) for 10 days plus nitrofurantoin (100 mg 3×/day) for 5 days in the presence of ESBL-E bacteriuria. The primary outcome was detection of ESBL-E by rectal swab  $28 \pm 7$  days after the end of treatment. Missing primary outcome data were imputed based on the last available observation. Additional cultures (rectal, inguinal and urine) were taken on day 6 of treatment and on days 1 and 7 post-treatment. The study protocol has been registered with ClinicalTrials.gov (NCT00826670).

**Results:** Among 54 patients (27 in each group) included in the primary analysis, there was no statistically significant difference between the groups with regard to the primary outcome [14/27 (52%) versus 10/27 (37%),  $P=0.27$ ]. During treatment and shortly afterwards, there was significantly lower rectal ESBL-E carriage in the treatment group: 9/26 versus 19/22 on day 6 of treatment ( $P<0.001$ ) and 8/25 versus 20/26 on day 1 post-treatment ( $P=0.001$ ). This effect had disappeared by day 7 post-treatment (18/27 versus 17/25,  $P=0.92$ ). Liquid stools were more common in the treatment group (7/27 versus 2/29,  $P=0.05$ ).

**Conclusions:** The regimen used in this study temporarily suppressed ESBL-E carriage, but had no long-term effect.

**Keywords:** multidrug-resistant organisms, polymyxins, aminoglycosides, nitrofurantoin, Switzerland

### Introduction

Intestinal carriage of extended-spectrum  $\beta$ -lactamase-producing Enterobacteriaceae (ESBL-E) has become common in many countries.<sup>1,2</sup> While ESBL-E carriage often persists for years without disease, these bacteria can occasionally cause bloodstream and urinary tract infections even in patients without discernible healthcare-associated risk factors.<sup>3–8</sup>

Examining methods to decolonize ESBL-E carriers as a prevention strategy seems warranted, given the risk of subsequent invasive infection in ESBL-E carriers, the fact that carriers are a potential source of cross-transmission, the potential for chronic

carriage and the possibility of horizontal gene transfer conferring resistance to other bacteria in the intestinal tract.<sup>9</sup> Since the intestinal tract is the main reservoir for ESBL-E, non-absorbed oral antibiotics without activity against the anaerobic microflora, such as aminoglycosides and polymyxins, are promising treatment options. These agents have been used widely for selective digestive decontamination in patients undergoing chemotherapy or intestinal surgery and in critically ill patients, and are generally well tolerated.<sup>10–12</sup>

While decolonization regimens have been extensively studied for Gram-positive bacteria such as *Staphylococcus aureus*, only a

few studies have examined the effect of decolonization attempts on ESBL-E carriage.<sup>13</sup> Most of these studies were uncontrolled and had important methodological limitations.<sup>14–17</sup> To our knowledge, no randomized, placebo-controlled clinical trial has been conducted to study the efficacy of a systematic ESBL-E eradication strategy. Eradication or suppression of ESBL-E carriage would theoretically be beneficial for both the individual patient and the community. However, the emergence of resistance to decolonization agents is a potential concern that needs to be monitored.<sup>18</sup> We performed an investigator-initiated, double-blind, placebo-controlled study to evaluate the efficacy and safety of an oral course of colistin and neomycin for 10 days (with nitrofurantoin in the case of ESBL-E bacteriuria) to suppress asymptomatic gastrointestinal ESBL-E carriage.

## Methods

### Trial design

This was a double-blind, placebo-controlled, parallel-group study with balanced (1:1) randomization. The study protocol was approved by the local institutional review board (IRB) (no. 08-161) and the Swiss agency for therapeutic products (SwissMedic no. 2009DR2087) and has been registered with ClinicalTrials.gov (NCT00826670). Written informed consent was obtained from all participants.

With regard to changes to methods after trial commencement, a positive urine culture with ESBL-E was initially considered an exclusion criterion. Due to slow recruitment, the protocol was, however, amended and from January 2010 onwards this was no longer an exclusion criterion except in the context of a urinary catheter that could not be changed.

### Participants

Enrolment occurred between June 2009 and June 2012. Patients aged  $\geq 18$  years with an ESBL-E-positive rectal swab and the ability to provide informed consent were eligible. An automatic alert system identifies all readmitted patients with a history of ESBL-E carriage at Geneva University Hospitals (HUG).<sup>19</sup> Active screening for ESBL-E carriage was limited to these 'alert' patients and certain pre-defined risk groups, such as patients transferred from abroad or patients having shared a room with newly detected ESBL-E carriers.<sup>20</sup> Patients with active ESBL-E infection and patients treated with antibiotics active against ESBL-E were excluded. Additional exclusion criteria were pregnancy/breastfeeding, contraindications to the use of the study drugs, previous study enrolment and resistance of the colonizing ESBL-E strain to colistin (defined as MIC  $> 2$  mg/L).

The study was conducted in all inpatient wards of HUG, a tertiary care centre with 1915 beds and  $\sim 48\,000$  yearly admissions in Switzerland.

### Interventions

Patients randomized to the treatment arm received oral colistin sulphate (50 mg equivalent to 42 mg colistin base or 1.26 million units 4 $\times$ /day) and oral neomycin sulphate (250 mg equivalent to 178 mg neomycin base 4 $\times$ /day) for 10 days. In the presence of ESBL-E bacteriuria, oral nitrofurantoin (100 mg 3 $\times$ /day) was added during the first 5 days. Patients in the control group received placebo drugs with the same frequency and duration of administration.

### Outcomes

Patients were assessed at baseline, on day 6 of treatment and on days 1, 7 and 28 after the end of treatment. At each visit, rectal swabs were performed by inserting a pre-moistened swab 3–4 cm past the anal sphincter, rotating the swab 360° and then inserting the swab immediately in culture

media. In addition, both inguinal folds were swabbed with a second pre-moistened swab. All patients provided a midstream urine sample at baseline and at the final follow-up visit. The pre-defined primary outcome of the study was the detection of intestinal ESBL-E carriage by a rectal swab during day  $28 \pm 7$  post-treatment. Secondary outcomes were safety and tolerability of the study regimen, detection of rectal, urinary and inguinal ESBL-E carriage during the other study visits, and change in colistin MICs between baseline and the final visit. Poor treatment compliance was defined as  $> 20\%$  of any of the study medication remaining in the study drug box when returned by the patient.

Screening for ESBL-E was performed using a selective chromogenic agar (BLSE-ID, bioMérieux, Marcy l'Étoile, France). Bacterial identification was based on the colour of the colonies with subsequent confirmation by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Billerica, MA, USA). ESBL production was confirmed by the double-disc synergy test. Until October 2011, four discs were used: cefotaxime, cefotaxime/clavulanic acid, ceftazidime and ceftazidime/clavulanic acid. The presence of ESBL was confirmed whenever the inhibition zone was  $\geq 5$  mm larger with the antibiotic/clavulanic acid combination than with the antibiotic alone, confirming synergy. From October 2011, only two discs were used: ceftazidime (30  $\mu$ g) and ceftazidime/clavulanic acid deposited 20 mm apart on a Mueller–Hinton agar plate. The presence of ESBL was confirmed whenever synergy was observed (inhibition zone increased by  $\geq 5$  mm). Susceptibility testing was performed using commercial panels and CLSI criteria (disc diffusion test for nitrofurantoin and Etest for colistin).<sup>21,22</sup> Neomycin MICs were determined as recommended *post hoc* for available baseline and day 28 post-treatment samples in the colistin/neomycin group and for a convenience sample of 17 patients in the placebo group (baseline only).<sup>23</sup>

### Sample size

Based on our own experience, we assumed that 30% of patients would clear ESBL-E colonization spontaneously within 28 days and hypothesized that a decolonization regimen would be clinically useful if able to clear colonization in an additional 40% of persons. Using a two-sided  $\alpha$  of 0.05 and a  $\beta$  of 0.2, we calculated a sample size of 29 patients in each group.

### Randomization

The randomization sequence was generated by the study pharmacist using an internet-based randomization plan generator with a constant block size of 10. Based on the randomization sequence, containers with the study drugs were sequentially numbered and participants were given containers in numerical order. Participants were enrolled by the physicians that were part of the study team.

### Blinding

The study pharmacist was the only individual aware of the treatment allocation and was not involved in the study conduct or analysis. The placebo capsules contained mannitol and were indistinguishable from the test medication with regard to colour, size and form. Participants, care providers and those assessing outcomes were blinded to the treatment allocation. The success of blinding was not formally assessed.

### Statistical methods

The primary analysis was a modified intention-to-treat analysis that excluded patients with no follow-up visit or a baseline rectal swab that was either negative or not performed. In the case of missing primary outcome data (e.g. due to loss to follow-up) or in the case of a final study visit that was performed either too late or too early (i.e.  $< 21$  days or  $> 35$  days after the end of the decolonization regimen), we imputed the

primary outcome based on the last available observation. Since imputation of missing outcomes may lead to biased results, we also performed a sensitivity analysis whereby patients with final assessment earlier than 21 days after the end of treatment were assigned a negative final rectal swab in the placebo group (since there is spontaneous loss of carriage over time) and a positive rectal swab in the treatment group (in case of a rebound effect). In addition, patients in the treatment group with a final assessment later than 35 days and/or treated with antibiotics active against ESBL-E were considered to have failed eradication.

Secondary outcome measures were evaluated including all participants with evaluable data at each respective study visit. All patients having received at least one dose of the study drug were included in the analysis of adverse effects. Differences in ESBL-E carriage between the study groups were analysed by the  $\chi^2$ -test or Fisher's exact test, as appropriate. Univariate

logistic regression was used to determine the OR for the presence of ESBL-E in the treatment group. The Wilcoxon signed-rank test was used to assess changes in colistin and neomycin MICs. All tests were two-tailed with a  $P$  value  $<0.05$  considered statistically significant. Statistical analyses were performed using STATA version 12 (Stata Corp., College Station, TX, USA).

Results

Participant flow and recruitment

The study flow chart is shown in Figure 1. There were 1281 patients with known current or past ESBL-E colonization at HUG between June 2009 and June 2012. Of these, 139 (10.9%) were deemed

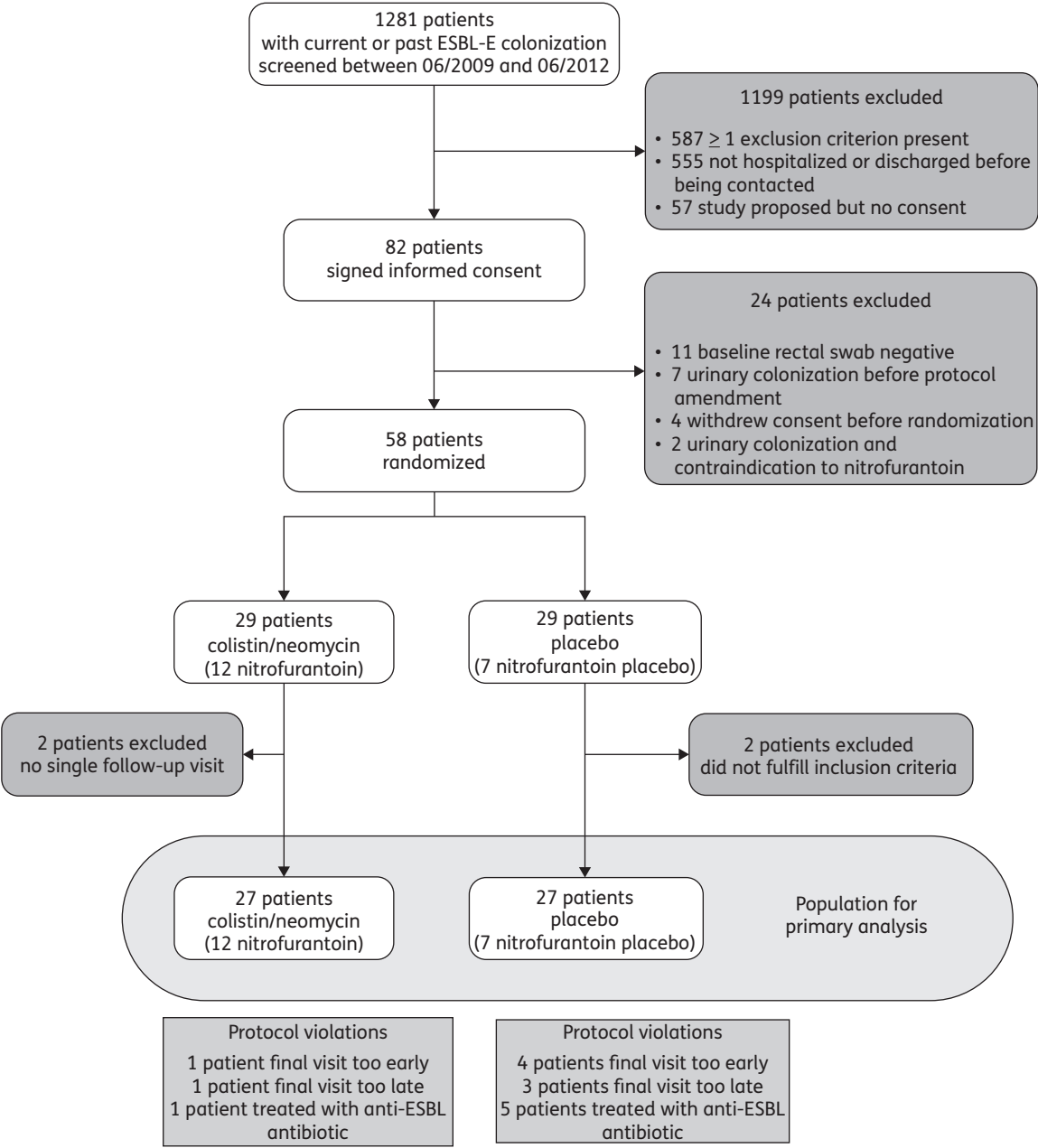


Figure 1. Trial profile.

to be eligible after chart review and were invited to participate. Eighty-two (6.4%) agreed to participate in the study and provided written consent. After the exclusion of 24 patients that were found not to meet the inclusion criteria after baseline assessment, 29 patients were randomized to each study arm.

### Baseline data

The two study groups had similar baseline clinical and demographic characteristics (Table 1). The mean age of participants was 54.5 years (range 19–81 years); 34/58 (58.6%) were male. More patients in the treatment group had bacteriuria (12/29 versus 7/29). Half of all patients had inguinal carriage at baseline. *Escherichia coli* was the predominant intestinal ESBL-E species, detected in 47/58 (81.0%) patients.

### Numbers analysed

Of the 58 patients, 2 (both in the treatment group) withdrew consent after randomization but before treatment start and were therefore excluded from further analysis. An additional two patients (both in the placebo group) were erroneously randomized based on ESBL-E carriage detected by stool culture (one had a negative rectal swab at baseline and one had no rectal swab performed). Both were excluded from the analysis of the primary outcome but were included in the other analyses. Twenty-seven patients in each group were included in the primary analysis. Of these, seven participants in the placebo group (two lost to follow-up, one withdrawal of consent and refusal of further follow-up and four logistic reasons) and two in the treatment group (one lost to follow-up and one logistic reasons) had a final assessment that was performed either too early or too late (Figure 1). For these patients, the primary outcome was imputed based on the last available result.

### Outcomes and estimation

In the primary analysis, 14 of 27 patients (51.9%) in the treatment group and 10 of 27 (37.0%) in the placebo group had eradicated ESBL-E carriage, a difference that was not statistically significant (OR 0.55, 95% CI 0.18–1.62). The conservative sensitivity analysis, which assigned a different outcome for four patients in the placebo group (since final analysis was too early) and for two patients in the treatment group (one with a final analysis performed too early and one treated with fosfomycin) confirmed the absence of an effect (OR 1.35, 95% CI 0.46–3.93).

Figure 2 displays the evolution of ESBL-E carriage over time, according to the carriage sites at baseline. On day 6 of treatment, rectal carriage of ESBL-E was significantly lower in the treatment group than in the placebo group (9/26 versus 19/22,  $P < 0.001$ ). This difference persisted until the visit 1 day after the end of treatment (8/25 versus 20/26,  $P = 0.001$ ), but had disappeared by the next visit at day 7 after the end of treatment (18/27 versus 17/25,  $P = 0.92$ ). There was no significant difference in inguinal carriage between the groups at any study visit. There was also no significant effect on bacteriuria with ESBL-E at any study visit in the subgroup of patients with bacteriuria at baseline.

### Harms

Seven out of 27 (25.9%) patients in the treatment group (versus 2/29 in the placebo group,  $P = 0.05$ ) with at least one follow-up visit

**Table 1.** Baseline demographics and microbiological results by group (all randomized patients)

	Colistin/neomycin group (n = 29)	Placebo group (n = 29)
Male, n (%)	18 (62.1)	16 (55.2)
Age (years), median (IQR)	51 (38–67)	61 (48–69)
Duration of known ESBL-E carriage at inclusion (days), median (IQR)	7 (6–21)	11 (7–54)
BMI (kg/m <sup>2</sup> ), median (IQR)	26.1 (23.3–28.4)	26.1 (23.1–29.0)
Comorbidities, n (%)		
cardiovascular disease	5 (17.2)	6 (20.7)
COPD	2 (6.9)	6 (20.7)
diabetes	6 (20.7)	6 (20.7)
chronic liver disease	1 (3.5)	2 (6.9)
neoplastic disease	1 (3.5)	1 (3.5)
immunosuppressive treatment	4 (13.8)	2 (6.9)
inflammatory bowel diseases	0	0
ESBL-E species at baseline rectal swab, n		
<i>Escherichia coli</i>	25	20
<i>Klebsiella pneumoniae</i>	9	5
<i>Klebsiella oxytoca</i>	1	0
<i>Citrobacter freundii</i>	0	1
<i>Enterobacter cloacae</i>	2	2
<i>Enterobacter asburiae</i>	0	1
none/unknown <sup>a</sup>	2	0
Two species at baseline rectal swab, n (%)	8 (27.6)	2 (6.9)
Site of ESBL-E colonization at baseline, n (%)		
rectal <sup>a</sup>	27 (93.1)	29 (100)
inguinal	15 (51.7)	14 (48.3)
urine	12 (41.4)	7 (24.1)
Baseline colistin MIC (mg/L) <sup>b</sup> , median (IQR)	0.190 (0.125–0.380)	0.125 (0.125–0.250)
Baseline neomycin MIC (mg/L), median (IQR)	2 (2–32)	2 <sup>c</sup> (2–32)

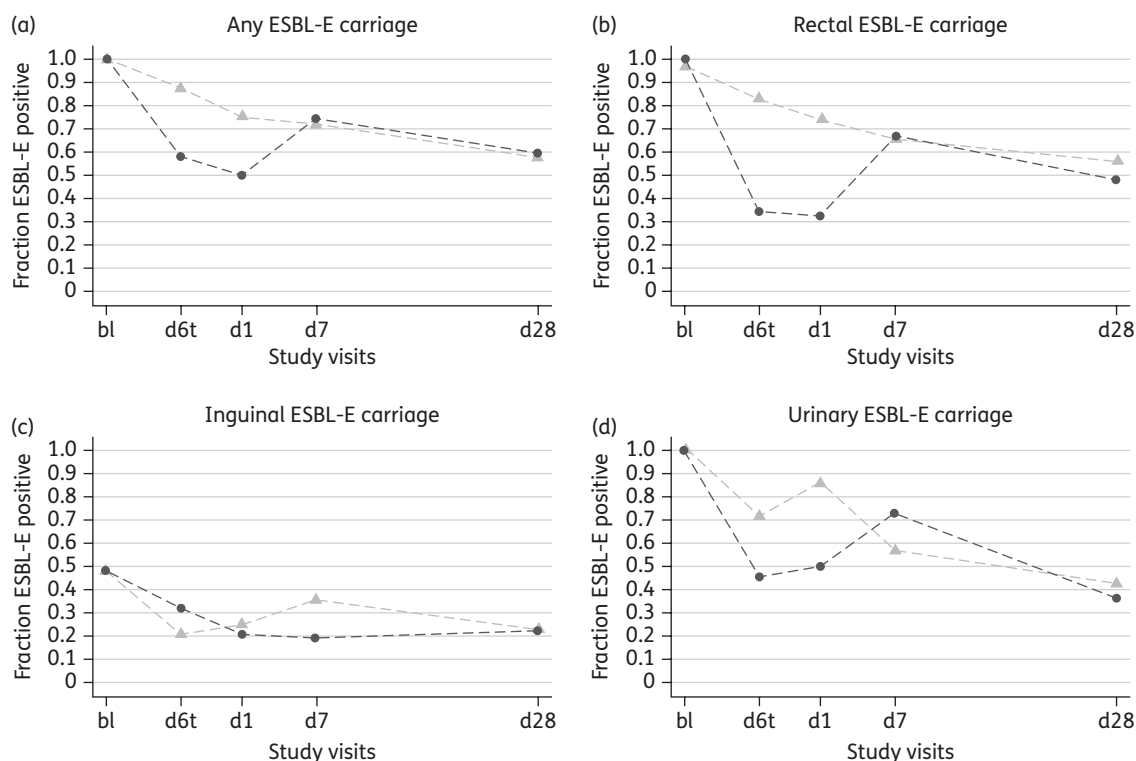
BMI, body mass index; COPD, chronic obstructive pulmonary disease.

<sup>a</sup>Two patients had positive stool cultures with ESBL-producing *E. coli*. One patient had a negative rectal baseline swab and one had no rectal swab performed.

<sup>b</sup>In case of more than one ESBL-E species in the same individual, the highest MIC was chosen.

<sup>c</sup>Convenience sample of 17/29 patients from the control group.

reported at least one episode of liquid stools. Two of these patients stopped treatment prematurely. A total of six patients were treated with antibiotics with activity against the colonizing ESBL-E strain before the end of follow-up (five in the placebo group and one in the treatment group).



**Figure 2.** Evolution of ESBL-E carriage over time with regard to (a) any ESBL-E carriage, (b) rectal ESBL-E carriage, (c) inguinal ESBL-E carriage and (d) urinary ESBL-E carriage. All graphs exclude two patients in the placebo group without a single follow-up visit. Study visits are reported with the scheduled visit date, even if done early or late. Graphs (a), (b) and (c) include all available data at each study visit. Graph (d) only includes participants with urinary ESBL-E colonization at baseline. Treatment, dark grey circles; placebo, light grey triangles. bl, baseline; d6t, day 6 of treatment; d1, day 1 post-treatment; d7, day 7 post-treatment; d28, day 28 post-treatment.

All ESBL-E isolates recovered during the study were susceptible to carbapenems. There was no statistically significant change in colistin or neomycin MICs between baseline and the final ESBL-E culture in the treatment group (Figure 3). In addition, with the exception of one isolate of an intrinsically colistin-resistant species (*Morganella morganii*), no colistin resistance was detected in the treatment group during follow-up.

### Treatment adherence

Boxes of study medication could be recuperated for 41 (71%) patients. All 18 patients in the placebo group with recuperated boxes fulfilled criteria for adherence. Of the 22 patients in the treatment group that had taken at least one dose of study medication with recuperated boxes, 3 patients had >20% of the study medication left, of whom 2 had stopped treatment prematurely (see above).

## Discussion

This randomized, controlled trial of an oral decolonization regimen demonstrated a substantial temporary suppression of intestinal ESBL-E carriage during treatment, with no sustained effect after 4 weeks.

### Previous studies

To our knowledge, we report the first randomized, controlled trial examining a decolonization strategy for carriers of ESBL-E. An Israeli study examined the effectiveness of selective digestive

decontamination for eradicating carriage of carbapenem-resistant *Klebsiella pneumoniae* (CRKP).<sup>24</sup> The interpretation of this study that reported a reduction in CRKP-positive rectal swabs at weeks 2 (16% versus 61%) and 6 (33% versus 59%) is made difficult by methodological limitations, and the fact that 9/40 patients died.

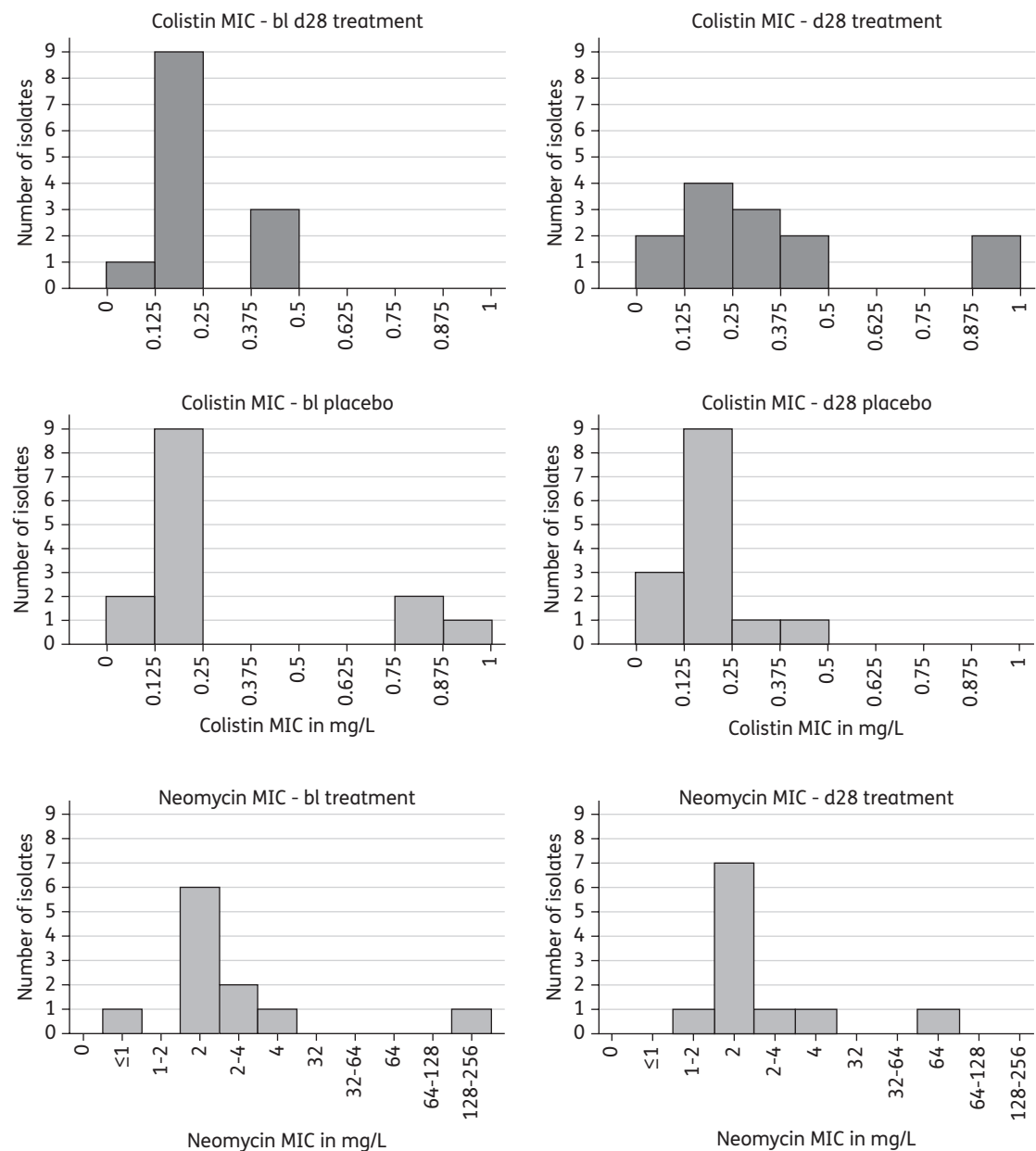
Another article reported the experience with ESBL-E decolonization at the University Hospital Basel between 2000 and 2008.<sup>25</sup> In this uncontrolled case series, all patients with documented ESBL-E colonization were offered a regimen consisting of chlorhexidine mouth rinse in case of throat colonization, oral paromomycin in case of intestinal colonization and oral antibiotics in case of bacteriuria. Of the 35 patients with available follow-up data, 63% were free of ESBL at the last follow-up performed. This percentage was, however, not significantly different from the 18 patients that did not receive decolonization treatment.

Several older studies have reported the use of different decolonization regimens in ESBL-E outbreaks with mixed results.<sup>14–17</sup> Since the interpretation of these studies is hampered by their weak study design, limited generalizability and very short follow-up periods, a detailed discussion is beyond the scope of this article.

### Extraintestinal colonization

In our study, the percentage of patients with inguinal ESBL-E colonization was 50% at baseline. This is similar to findings from two other Swiss hospitals.<sup>26,27</sup> It remains unclear if the skin represents a separate reservoir for ESBL-E and if adding a skin disinfectant to





**Figure 3.** Colistin and neomycin MICs at baseline and at the final [day 28 post-treatment (d28)] study visit by treatment group. Graphs only include instances where the same ESBL-E was recovered on rectal swabs or stool cultures at baseline and at the final study visit and where a colistin MIC was determined at both visits. bl, baseline.

the decolonization regimen may provide any additional benefit. Pharyngeal carriage of ESBL-E has also been described and may yet represent a further reservoir.<sup>28</sup>

**Colistin resistance**

We did not observe statistically significant changes in the measured colistin MIC values between the initial and final isolates, and no acquired colistin resistance was documented in isolates obtained during follow-up.

**Limitations and generalizability**

First, we deviated from the intention-to-treat principle in our analyses by excluding four patients after randomization.<sup>29</sup> We have, however, no reason to suspect that the motives for the exclusions were related in any way to group assignment. Second, the administered dose of 1 g of neomycin sulphate per day was relatively low compared with the 3–4 g per day commonly used in pre-operative bowel preparation.<sup>10</sup> Other centres, however, have used doses similar to ours for selective gut decontamination.<sup>30</sup> Third, rectal swabs may be inadequate to detect resistant pathogens present

in small amounts and stool cultures may have given different results.<sup>31</sup> A negative rectal swab may therefore reflect suppression of ESBL-E colonies below the detection level rather than complete eradication of ESBL-E carriage. In addition, the absence of growth on selective chromogenic agar during treatment may be due to the inhibitory effect of the antibiotics (rather than the absence of ESBL-E). Fourth, the trial was underpowered to detect clinically significant differences between the treatment arms that were smaller than those postulated for the sample size calculation. Fifth, we were unable to differentiate rebound of colonization from exogenous reacquisition of ESBL-E strains. Finally, the external validity of this trial may be limited given its single-centre setting and highly selected patient population.

### Interpretation

Intestinal ESBL-E carriage is a risk factor for subsequent bacteraemia and invasive urinary tract infection, particularly among high-risk patients.<sup>32</sup> Temporary suppression of ESBL-E carriage could add a clinical benefit in high-risk patients. Thus, a strategy of early detection and suppression of ESBL-E in colonized high-risk patients during prolonged periods of immunosuppression or derangement of gastrointestinal mucosal integrity could result in a reduction in the incidence of subsequent ESBL-E bloodstream infections. A large multicentre trial would be needed to test this hypothesis. The increasing frequency of ESBL-E carriage in the general population, possibly mediated by contaminated food, likely renders a widespread decolonization policy for ESBL carriers unfeasible.<sup>33,34</sup> Furthermore, the long-term impact of decolonization regimens on the intestinal microbiome and the emergence of colistin resistance merit further investigation.<sup>35</sup>

### Conclusion

This study did not demonstrate an effect of an oral antibiotic regimen containing colistin and neomycin, with nitrofurantoin in presence of bacteriuria, on rectal ESBL-E carriage 28 days after the end of treatment. We observed a temporary suppression of ESBL-E carriage during treatment and immediately afterwards, with rapid rebound 1 week after the end of treatment. Future studies should attempt to define patient populations at high risk of infection or pathogens at high risk of cross-transmission, where this transient effect may be beneficial. Additionally, different strategies warrant investigation, such as administering probiotics at the conclusion of the decolonization regimen.

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### Transparency declarations

A. Andremont is co-founder and president of the scientific board of Da Volterra under the frame of the French law for innovation and research. J. S. is part-time chief medical advisor for bioMérieux. S. H. is a member of the scientific advisory board of bioMérieux and Da Volterra. All other authors: none to declare.

The study protocol is available upon request

### Author contributions

Agree with the manuscript's results and conclusions: all authors. Developed the original idea for the study: S. H. Oversight of study integrity as Chief Investigator: S. H. Designed the study: B. H. and S. H. Analysed the data: B. H. Collected data/did experiments for the study: B. H., T. H., A. Agostinho, G. R. and A. Andremont. Enrolled patients: B. H., T. H., I. U. and S. H. Wrote the first draft of the paper: B. H. and S. H. Contributed to the writing of the paper and interpretation of study findings: all authors.

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